

Application No. 10/127,585

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OFFICIAL**RESPONSE UNDER 37 CFR §1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1631****IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re the Application of

James N. CAWSE

Group Art Unit: 1631

Application No.: 09/938,763

Examiner: Cheyne D. Ly

Filed: August 27, 2001

For: METHOD AND SYSTEM TO INVESTIGATE A COMPLEX
CHEMICAL SPACE**FACSIMILE TRANSMITTAL COVER SHEET**To: Examiner: Cheyne D. Ly
Group Art Unit: 1631
TC 1600 (After Final)

This transmission includes 17 pages (including cover sheet). When facsimile receipt is returned with this cover sheet, the USPTO acknowledges receiving the following documents:

- 1) REQUEST FOR RECONSIDERATION (12 pages)
- 2) REQUEST TO WITHDRAW FINAL REJECTION (4 pages)

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12 MARCH 2004

Application No. 09/938,763

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**RESPONSE UNDER 37 CFR §1.116
EXPEDITED PROCEDURE
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For: **METHOD AND SYSTEM TO INVESTIGATE A COMPLEX
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REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. §1.116

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Commissioner for Patents
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Sir:

Claims 1 to 7, 9 to 10, 13 to 15, 17 to 36 and 39 to 42 are pending. The February 24, 2004 Final Rejection rejected claims 1 to 7, 9 to 10, 13 to 15, 17 to 36 and 39 to 42 under 35 U.S.C. 112, second paragraph; under 35 U.S.C. 112, first paragraph; and under 35 U.S.C. 103(a). Reconsideration is requested for the following reasons.

I. 35 U.S.C. 112, SECOND PARAGRAPH REJECTION

Claims 1 to 7, 9 to 10, 13 to 15, 17 to 36 and 39 to 42 were rejected under 35 U.S.C. §112, second paragraph.

35 U.S.C. §112, second paragraph, provides:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Whether claims are definite under 35 U.S.C. §112, second paragraph, is determined in light of the specification. The claims read in light of the specification need

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only apprise those skilled in the art of the scope of the invention. *Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1387, 231 USPQ 81, 94, 95 (Fed. Cir. 1986), cert. denied 480 US 947 (1987).

The specification defines factors of a catalyst system at paragraphs [0043], [0044] and in the EXAMPLES. The factor conditions are described in detail in the EXAMPLES. One skilled in the art is clearly apprised of the scope of the invention. The phrase "the factors comprise a catalyst system and conditions" is very accepted, conventional claim language, well known to one skilled in the art. See *In re Janakirama-Rao*, 317 F.2d 951, 137 USPQ 893 (CCPA 1963).

Claims 1 to 7, 9 to 10, 13 to 15, 17 to 36 and 39 to 42 distinctly claim the invention and the rejection under 35 U.S.C. 112, second paragraph should be withdrawn.

II. 35 U.S.C. 112, FIRST PARAGRAPH REJECTION

Claims 1 to 7, 9 to 10, 13 to 15, 17 to 36 and 39 to 42 were rejected under 35 U.S.C. §112, first paragraph.

The February 24, 2004 Final Rejection acknowledges that the term "greater or less than" is included within the term "outside of." The term "greater or less than the standard deviation" is shown in the EXAMPLES and described in the specification with reference to "outside." The term "greater or less" is found in 285 patents of the USPTO data base. The written description of the specification clearly teaches "identifying" "greater or less than the standard deviation" to one skilled in the art. The rejection of claims 1 to 7, 9 to 10, 13 to 15, 17 to 36 and 39 to 42 were rejected under 35 U.S.C. §112, first paragraph should be withdrawn.

III. 35 U.S.C. 103(a) REJECTIONS

Claims 1 to 7, 9 to 10, 13 to 15, 17 to 36 and 39 to 42 were rejected under 35 U.S.C. §103(a) over Agrafiotis et al., Grate et al. and Chaudhari et al.

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A. IMPROPER COMBINATION OF REFERENCES-NON ANALOGOUS ART

The Agrafiotis et al reference relates to a synthesis protocol with re-iterated synthesis steps based on "structure-activity models" (Abstract). Grate et al. discloses "analyzing [a] sample with a multivariate instrument," for example, acoustic wave sensors (col. 9, lines 56 to 65). Chaudhari et al. is a commonly assigned patent that teaches reacting a hydroxyaromatic compound with oxygen and carbon monoxide in the presence of a VIIIB catalyst to synthesize a diaryl carbonate (Abstract).

"{Analyzing [a] sample with a multivariate instrument" (Grate et al.) and a "diaryl carbonate synthesis method (Chaudhari et al.) are unrelated, disparate arts, not "reasonably pertinent" to one another or to a method of defining an experimental space for a CHTS method. The references are not properly combinable with the Agrafiotis et al reference as analogous art. *See In re Clay*, 23 USPQ2d 1058, 1060 (Fed. Cir. 1992).

The February 24, 2004 Final Rejection page 5 states:

... Agrafiotis et al. discloses a method of analyzing chemical properties in a sample for performing searches in chemical libraries to identify chemical compounds (Abstract etc. and column 3, lines 31-40), Grate et al. discloses a method for analyzing and generating chemical compounds (Abstract etc.), and Chaudhari et al. discloses a method for analyzing and selection chemicals (Abstract etc.). Therefore, the citations above adequately support that one of ordinary skill in the art at the time of the instant invention would look into the references of Agrafiotis et al., Grate et al., and Chaudhari et al. to address the need to generate chemical entities using defined chemical properties.

Applicant fails to understand this argument. Is the PTO arguing that the references are analogous art because each reference includes the word "chemical" or addresses a "chemical" concept?

The claimed invention is not broadly directed to "chemical." The claimed invention is directed to defining an experimental space of a catalyzed chemical reaction and effecting a CHTS method on the space, (claim 1). The relevant question in the combination, is in what manner are references that disclose "analyzing [a] sample with a multivariate instrument" (Grate et al.) and a diaryl carbonate synthesis method

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(Chaudhari et al.) "reasonably pertinent" to a method of defining an experimental space for a CHTS method. *See In re Clay*, 23 USPQ2d 1058, 1060 (Fed. Cir. 1992). That the references are related to "chemical" does not address the question.

The references are non-analogous art. The rejections are supportable only through hindsight. *See In re Deuel*, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995). For this reason alone, the rejection of claims 1 to 7, 9 to 10, 13 to 15, 17 to 36 and 39 to 42 35 U.S.C. 103(a) over Agrafiotis et al., Grate et al. and Chaudhari et al. must be withdrawn.

B. IMPROPER COMBINATION OF REFERENCES-NO REASON TO COMBINE

To support a rejection based on a combination of references, "[t]he PTO "must not only assure that... requisite findings are made, based on evidence of record, but must also *explain the reasoning by which the findings are deemed to support the agency's conclusion*" (emphasis added). *In re Lee*, 277 F.3d 1338, 1343, 61 USPQ2d 1430, 1434 (Fed. Cir. 2002).

In response to this important requirement, the February 24, 2004 Final Rejection substantially repeats its previous argument. At page 6, the Final Rejection states:

Agrafiotis et al. suggests an improvement by disclosing the need for a system and method for efficiently and effectively generating new leads designed for specific utilities. Further, the suggested improvement is directed to generating chemical compounds with desire [sic] physical, chemical, and/or biological properties via structure activity models (column 3, lines 27-55).

First, the PTO incorrectly characterizes the Agrafiotis et al teaching. The Agrafiotis et al. teaching at col. 3, lines 13 (to complete the sentence) to 55 is:

Furthermore, the real issues of structural and function group diversity are still not directly addressed; bioactive agents such as drugs and agricultural products possess diversity that could never be achieved with available peptide and oligonucleotide libraries since the available peptide and oligonucleotide components only possess limited functional group diversity and limited topology imposed through the inherent nature of the available components. Thus, the difficulties associated with synthesizing variants of lead compounds are exacerbated by using typical peptide and

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oligonucleotide combinatorial chemical libraries to produce such lead compounds. The issues described above are not limited to bioactive agents but rather to any lead generating paradigm for which a chemical agent of defined and specific activity is desired.

Thus, the need remains for a system and method for efficiently and effectively generating new leads designed for specific utilities.

SUMMARY OF THE INVENTION

The present invention is directed to a computer based system and method for automatically generating chemical entities with desired physical, chemical and/or biological properties. The present invention is also directed to the chemical entities produced by this system and method. For purposes of illustration, the present invention is described herein with respect to the production of drug leads. However, the present invention is not limited to this embodiment.

Specifically, the present invention is directed to an iterative process for generating new chemical compounds with a prescribed set of physical, chemical and/or biological properties, and to a system for implementing this process. During each iteration of the process, (1) a directed diversity chemical library is robotically generated in accordance with robotic synthesis instructions; (2) the compounds in the directed diversity chemical library are analyzed under computer control, and structure-activity/structure-property models (collectively referred to as structure-activity models hereafter) are constructed and/or refined; and (3) new robotic synthesis instructions are generated to control the synthesis of the directed diversity chemical library for the next iteration.

The substance of the Agrafiotis et al teaching from the quoted passage is that there is a "need for a system and method" to investigate "peptide and oligonucleotide component(s)" and that Agrafiotis et al addresses this need by providing an "iterative process" invention "for generating new chemical compounds." This is not an expression of a need for "analyzing [a] sample with a multivariate instrument" (Grate et al.) teaching or "diaryl carbonate synthesis method" teaching (Chaudhari et al.) of the references that are combined in the PTO 35 U.S.C. §103(a) rejection. Further, the quoted Agrafiotis et al disclosure teaches away from the Grate et al combination and the Chaudhari et al. combination by teaching that the Agrafiotis et al. invention already addresses the expresses "need."

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Further at page 6, the Final Rejection concludes:

Therefore, the improvement suggested by Agrafiotis et al. would motivate one of ordinary skill in the art to apply a tool, matrix algebra, for characterizing chemical properties as taught by Grate et al, to the method of Agrafiotis et al. to disclose the invention of the instant application. Further, the improvement suggested by Agrafiotis et al. would motivate one of skill in the art to apply a tool, matrix algebra, for characterizing a catalyst as taught by Grate et al. and Chaudhari et al.

First, the PTO statement is incorrect to any extent that it implies that "Grate et al. and Chaudhari et al." teach "matrix algebra, for characterizing a catalyst." There is no such teaching or suggestion in either reference. If the PTO disagrees, the PTO is respectfully requested to identify such teaching in either reference.

Second, the Agrafiotis et al expressed "need" is not for any of the Grate et al. "multivariate instrument" invention or the Chaudhari et al. or "diaryl carbonate synthesis method" invention. The PTO quoted Agrafiotis et al. need is for "a system and method" to investigate "peptide and oligonucleotide component(s)." systems.

The PTO "reason to combine" arguments are only conclusions without logic. Merely stating "[t]herefore, the improvement suggested by Agrafiotis et al. would motivate one of ordinary skill in the art to apply a tool, matrix algebra, for characterizing chemical properties as taught by Grate et al," and "would motivate one of skill in the art to apply a tool, matrix algebra, for characterizing a catalyst as taught by Grate et al. and Chaudhari et al." are not the *In re Lee* reasoning required to support a combination rejection.

The PTO is unable to provide the required *In re Lee* reasoning to combine because the references do not teach reasoning to combine. The 35 U.S.C. §103(a) rejection is based on a selective picking and choosing of features in secondary references, without any basis in the references for doing so. See *In re Deuel*, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995). The combination rejection of claims 1 to 7, 9 to 10, 13 to 15, 17 to 36 and 39 to 42 were rejected under 35 U.S.C. 103(a) over Agrafiotis et al., Grate et al. and Chaudhari et al. should be withdrawn.

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C. NO *PRIMA FACIE* CASE

Further as previously argued, even improperly combined, the references do not establish a *prima facie* case of obviousness of (1) defining an experimental space of a catalyzed chemical reaction to represent at least three factor interactions, "wherein the factors comprise a catalyst system and conditions" (all claims).

The February 24, 2004 Final Rejection page 7 states:

Specific to Applicant's argument by amendment ("wherein the factors comprise a catalyst system and conditions"), said amendment has been fully considered and found to be unpersuasive due to the vague and indefinite issue caused by said amendment.

An outstanding 35 U.S.C. §112, second paragraph rejection does not relieve the PTO from the *prima facie* prerequisite to applying a 35 U.S.C. §103(a) rejection. Applicant specifically requests the PTO to cite its authority for this position. Otherwise, the PTO must reissue the present Office Action to address the failure of the references to establish a *prima facie* case of obviousness of (1) defining an experimental space of a catalyzed chemical reaction to represent at least three factor interactions, "wherein the factors comprise a catalyst system and conditions" (all claims) or withdraw the 35 U.S.C. §103(a) rejection.

Additionally, Applicant's October 7, 2003 and December 17, 2003 responses argued that the references do not establish a *prima facie* case of (2) analyzing combinatorial results according to matrix algebra to select a best case set of factor levels from a *catalyzed experimental space* (claims 1 to 7 and 18 to 33); (3) conducting a CHTS on qualitative and quantitative factors (claim 35); (4) a programmed controller that analyzes CHTS results *according to matrix algebra* (claims 36, 39 and 41); (5) defining a space to represent "at least 6 orders of interaction of factors" of a *catalyzed chemical reaction* (claim 5); (6) defining a space to represent "at least 6 orders of interaction of factors" of a *catalyzed chemical reaction* (claim 6); (6) analyzing *combinatorial results* according a relationship $y = X\beta + e$ where X is a matrix of experiment factor and interaction levels, y is a matrix of experimental results, β is effects and e is an error term

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of variance σ^2 from a normal distribution (claim 18); (7) assembling results as an $n \times 1$ vector y , assembling factor level values into an $n \times k+1$ matrix X , representing extents of the results and factor level values as +1's and -1's accordingly and solving for *effects parameters* β according to the relationship $\beta = (X'X)^{-1}X'y$ where superscript ' is a transpose of a matrix and superscript $^{-1}$ identifies an inverse function of a matrix (claims 19 to 21); (8) reacting and identifying tagged reactants and products (claim 25); (9) reiterating a CHTS on an experimental space selected by matrix algebra analysis of first iteration results (claims 26 to 28); and (10) defining an experimental space to "comprise a reactant or catalyst at least partially embodied in a liquid and... contacting the reactant or catalyst with an additional reactant at least partially embodied in a gas, wherein the liquid forms a film having a thickness sufficient to allow a reaction rate that is essentially independent of a mass transfer rate of additional reactant into the liquid to synthesize products that comprise the results" (claim 34).

The PTO purports to respond to (2) to (10) at pages 7 to 12. However, none of pages 7 through 12 addresses the specific claim language identified in (2) through (10). Applicant has presented arguments (2) through (10) in his October 22, 2003 Request for Reconsideration and in his December 17, 2003 Amendment. The PTO has not responded. This is improper examination.

While the Office Action does mention some of the key words in Applicant's argument, the October 29 Office Action and now the Final Rejection fail to properly address the invention as defined by the claims. *See Allen Eng. Corp. v. Bartell Indus, Inc.* No. 01-1238 (Fed. Cir. Aug. 1, 2002)

For example, the Final Rejection states:

Specific to Applicant's argument that the "controller" in the Agrafiotis et al. reference is distinct from that of the instant invention, said argument has been fully considered and found to be unpersuasive as discussed below. Agrafiotis et al. discloses a computer system comprising a processor and controller as depicted in Figure 1; further, said system performs the computer-aided generation of chemical entities with prescribed set of physical, chemical and/or bioactive properties using a diversity of chemical libraries (column 4, line 65 to column 5, line 5). Grate et al. discloses the use of matrix algebra for characterizing,

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classifying, and identifying unknowns in a sample (Column 14, equation 10). The system of Agrafiotis et al. comprising a processor and controller for the generation of chemical entities and the matrix algebra for characterizing, classifying, and identifying unknowns in a sample of Grate et al. in combination discloses the limitations of claim 39 which depends from claim 36.

Final Rejection page 8.

However, claim 36 does not just claim a "controller" or a "processor and controller for the generation of chemical entities and the matrix algebra for characterizing, classifying, and identifying unknowns in a sample...." Claim 36 claims a "programmed controller that a programmed controller that a programmed controller that (A) represents the results as an $n \times 1$ matrix y where $n =$ a number of factor level combinations in the experiment; (B) represents extents of the factor level combinations in an $n \times n$ matrix X ; (C) solves n simultaneous equations represented by the matrices according to matrix algebra to form a results matrix β ; (D) represents the results matrix β as a normal probability plot; (E) defines a standard deviation for a result of the plot wherein the standard deviation represents a probability that a result deviation from the standard is random and that a positive interaction can be identified greater or less than the deviation; and (F) identifies the positive interaction greater or less than the standard deviation to identify an effect greater or less than the standard deviation that represents a best case set of factor levels from the catalyzed experimental space."

" Where, anywhere in the references is there a teaching of claim 36?

"A prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art...." *In re Rijckaert*, 28 USPQ2d 1955, 1956 (Fed. Cir. 1992). Agrafiotis et al., Grate et al. and Chaudhari et al. fail to teach or suggest any of (1) through (11) above. "If examination... does not produce a prima facie case of unpatentability, then without more the applicant is entitled to grant of the patent." *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

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Again, with respect to all of (1) through (10), the Office Action fails to point out where teachings of these limitations appear in the prior art references. Indeed, (1) through (10) do not appear in the references. The PTO has not established a *prima facie* case of obviousness of (1) through (10).

The PTO is respectfully requested to allow the claims or withdraw the present office action and to issue a new non-final office action that responds to all Applicant's arguments, restarting the period for response.

D. REJECTION BURDEN OF PROOF

The Office Action states that "Applicant's arguments have been fully considered and found to be *unpersuasive*" (Final Rejection page 5); "Applicant's argument (via questions) have been fully considered and found to be *unpersuasive as discussed below*" (Final Rejection page 6); "Applicant's arguments have been fully considered and found to be *unpersuasive as discussed below*" (Final Rejection page 7); and "[s]pecific to Applicant's argument that the "controller" in the Agrafiotis et al, reference is distinct from that of the instant invention, said argument has been fully considered and found to be *unpersuasive as discussed below*" (Final Rejection page 8).

However, persuasiveness of Applicant's argument is not the issue. The 35 U.S.C. 103(a) rejections are based on 35 U.S.C. 102(a) stating "A person *shall* be entitled to a patent *unless* (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent..." (emphasis added). A patent must be issued *unless* the PTO establishes a reason not to issue the patent; for example, by establishing a *prima facie* case of obviousness.

With respect to a *prima facie* case, MPEP 2142 points out that:

.... The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness.

MPEP 2142.

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Hence, the issue is not whether "Applicant's argument has been found to be unpersuasive." The issue is whether the PTO has met its burden of establishing a *prima facie* case of obviousness. Weighing persuasiveness of Applicant's arguments instead of meeting its *prima facie* burden, applies an incorrect burden of proof is improper examination.

IV. PREMATURE FINAL REJECTION

The office action is a premature final rejection. The PTO has not examined the claims according to a proper 35 U.S.C. §103(a) proof standard. The PTO has failed to address the (1) to (10) claim limitations as required by law.

The MPEP 2271 states:

.... The grounds of rejection must (in the final rejection) be clearly developed to such an extent that the patent owner may readily judge the advisability of an appeal.....

Further, 37 C.F.R. § 1.104 entitled "Nature of Examination" provides that "[t]he examiner's action will be complete as to all matters...."

In this respect, Applicants include with this Amendment, an MPEP 706.07(c) AND MPEP 706.07(d) REQUEST TO WITHDRAW FINAL REJECTION addressed to the Primary Examiner.

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V. CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that claims 1 to 7, 9 to 10, 13 to 15, 17 to 36 and 39 to 42 are allowable. Reconsideration and allowance are requested.

Should the Examiner believe that any further action is necessary in order to place this application in condition for allowance, he is requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,



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